REMARKS

Claims 22, 23, 25-35, and 37-58 are pending. Claims 24, 29, and 36 have been cancelled. Claim 24 is re-presented as independent claim 42. Claim 29 is re-presented as independent claim 47. Claim 36 is re-presented as independent claim 50. Claim 34 has been amended. Support for the amendment to claim 34 can be found on page 7, line 3 of the specification. Claims 40-58 are based on original claims 22-39, and incorporate the limitation that the compositions and methods be directed to human cells. No new matter has been added.

Rejections under 35 U.S.C. § 112

Claims 22-39 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one to use the invention as claimed. The Examiner states

> "the specification does not provide an enabling disclosure for the induction of tolerance to allogeneic tissue comprising re-introducing hematopoietic stem cells from a recipient which have been modified to express an allogeneic MHC class I antigen into said recipient animal...the specification does not provide sufficient guidance for inducing tolerance to a donor allograft by re-introducing recipient cells...the skilled artisan would not have had a reasonable expectation that a single MHC class I allele could tolerize T cells which recognize epitopes from other class I or class II alleles. Further, at the time of filing, it was well known that in the absence of immunosuppressive therapy, even a single MHC mismatch can result in rejection of the transplanted tissue."

Applicant respectfully traverses this rejection. Claims 22-39 are directed to bone marrow hematopoietic stem cells into which DNA encoding an MHC class I antigen of a nonidentical donor of the same species has been inserted, and methods of using such cells.

First of all, the claimed cells and methods are not directed to inducing tolerance to every donor antigen or to suppressing every recipient immune response to donor antigens. On the contrary, the claimed cells and methods are directed to those that inhibit a recipient's ability to mount an immune response against a donor antigen, MHC class I. See, for example, claim 34, which is directed to:

> "a method for inhibiting a mammalian recipient's ability to mount an immune response against an MHC class I antigen of tissue from a donor mammal of the same species to be provided to said recipient, comprising: providing said recipient with a cell composition comprising recipient species bone marrow hematopoietic stem cells having inserted therein DNA encoding an MHC class I antigen to be expressed in said recipient, said MHC class I antigen being the same as or closely related to that expressed by donor tissue to be provided to said recipient, to thereby inhibit said recipient's ability to mount an immune response against said MHC class I antigen expressed by the donor tissues." (emphasis added).

The specfication provides a working example in which cells engineered to express a class I antigen are used to inhibit a recipient immune response against the class I antigen. As shown in the specification, the claimed cells and methods are enabled. The experiments with congenic mice described in Example 3 demonstrate that hematopoietic cells transduced with a donor MHC class I allele inhibit the rejection of skin grafts by MHC-mismatched murine hosts (see pages 24-28 of the specification). Mice which received bone marrow cells transduced with the donor MHC class I allele, K^b, showed significantly prolonged acceptance of K^b-expressing skin grafts relative to mice which received non-transduced bone marrow (see Figure 7B of the specification). These data show that inhibition of an immune response to the transduced MHC class I is clearly induced in the absence of other confounding responses.

They Examiner argues that the mammalian trials in the specification, because they use congenic animals, do not support enablement:

> "The specification's working examples utilize two congenic strains of mice which are genetically identical except for a single MHC class I disparity. The examples demonstrate the transduction of hematopoietic stem cells from the first strain with a retrovirus encoding the disparate MHC class I allele (K^b), and the administration of these cells to lethally irradiated mice of the first strain followed by transplantation of skin from the congenic mouse strain resulting in prolongation of the graft survival compared to control mice. Unlike the Applicant's congenic model system, allogeneic transplantation involves multiple MHC class I and class II disparities, not to mention minor histocompatibility differences. The applicant's working examples do not demonstrate that a single class I allele can tolerize the spectrum of T cells which recognize all the different MHC antigens expressed by the donor mammal. As T cell tolerance, like T cell activation, is an antigen-specific event, the skilled artisan would not have had a

reasonable expectation that a single MHC class I allele could tolerize T cells which recognize epitopes from other class I or class II alleles."

The working example shows unambiguously that the donor response to the class I antigen was inhibited. Congenic mice strains allow one to observe the inhibition of the response against the class I antigen in the absence of responses to other antigens. This does not change the fact that very significant and robust inhibition of the recipient's response to the target class I antigen was achieved, showing that the claimed invention is enabled. The absence of other mismatched loci in no way questions, compromises, or casts doubt on the fact that the methods of the invention induced a very significant and robust inhibition of the recipient's immune response to the antigen. The applicant does not argue that there would not be responses to other antigens if other loci were mismatched in an allogeneic transplant. But, as is discussed below, the inventon is not directed to the complete inhibition of all recipient responses, but is rather focused on one aspect of the overall response.

Even if the Examiner is correct, and the "prevention of rejection" requires inhibition or suppression of multiple components, the invention, as claimed, is enabled. The claims do not require the complete suppression of all aspects of a recipient response against the donor organ. On the contrary, the claims are directed to cells and methods that inhibit an immune response against a very specfic (though very important) antigen, on an allograft. See claims 23, 30, 34, 41, 46, and 50, which are directed to cells and methods for inhibiting a recipient's immune response to a tissue.

The existence of other issues that a clinician needs to address to achieve clinical success, e.g., suppression of other rejection responses, providing appropriate anesthesia, controlling bleeding at the incision where the donor organ is placed, etc., does not mean that the claimed invention is unpatentable. Enablement does not require that a method or an agent give a complete and total clinical success (unless that is claimed). For example, an anti-proliferative drug may be useful, and more critical to the instant inquiry, enabled, as a cancer chemotherapy agent even though that drug, in complete isolation, might not provide a clinically acceptable

treatment. When combined with other drugs or other treatments, e.g., radiation treatments, it can be a useful and clinically successful drug.

In addition, there could be situations in which a donor and recipient had MHC haplotypes that differ only at a single class I allele (e.g., among sibling donor-recipient combinations). In this case, there would be only one MHC allele to induce tolerance to. As the Examiner is aware, this antigenic mismatch alone is a major barrier to successful engraftment. Even by the improperly high standard of enablement used in the rejection this embodiment is clearly enabled, rendering the cell and method claims patentable. Furthermore, in situations where it is desirable to induce tolerance against more than one MHC class I molecule, the methods of using hematopoietic stem cells transduced with an MHC class I molecule could simply be repeated with a cell which expresses a second class I antigen so that tolerance to both MHC class I antigens could be induced. Again, even by the improperly high standard of enablement applied in the rejection this embodiment is enabled.

The Examiner's statement that "the specification does not provide an alternate use for the disclosed cells other than their use in preventing transplant rejection" (emphasis added) is incorrect. The use is inhibiting a response to an antigen. Furthermore, even by the improperly high standard of enablement set out in the rejection the two uses described just above are enabled and thus there is an enabled utility for cells and methods. Accordingly, withdrawal of the rejection of claims 22-39 as non-enabled is requested.

Rejections under 35 U.S.C. § 103

Claims 22, 23, and 28 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen et al. in view of Pullen et al. Madsen et al. teaches H-2^k murine L cells transfected with MHC class I or class II alleles from an H-2^b mouse. Pullen et al. teaches the transfection of murine bone marrow with an MHC class II gene.

The Examiner states "Madsen et al. provides motivation for transfecting cells with either class I or class II genes of a different haplotype..." The Examiner acknowledges, "Madsen et al. does not teach the transfection of hematopoietic stem cells with either MHC class I or class II."

Madsen et al. teaches L cells, which are fibroblasts. Fibroblasts are not hematopoietic cells, much less are they hematopoietic stem cells.

With regard to Pullen, the Examiner argues,

> "Pullen et al. supplements Madsen et al. by teaching the transfection of murine H-2^b bone marrow, which contains hematopoietic stem cells, with the murine MHC class II Eα^d gene...Thus based on the motivation to use bone marrow stem cells for genetic manipulation provided by Pullen et al., and the motivation to transfect cells with the MHC class I or II genes of a different haplotype provided by Madsen et al., it would have been prima facie obvious...to transfect hematopoietic stem cells with genes for MHC class I of a different haplotype."

There is no motivation in the combination to transform hemopoeitic stem cells. The Examiner argues that Pullen provides motivation by "teaching that bone marrow is an excellent population of stem cells for genetic manipulation". Pullen et al. does not suggest the use of transformation of hematopoietic stem cells. Rather, Pullen et al. is about using macrophages to study gene expression, as is set out in the title of the paper, "Bone Marrow-derived Macrophage Expression of Endogenous and Transfected Class II MHC Genes During Differentiation In Vitro". In addition, Pullen et al. says nothing about MHC class I genes. Other than the fact that cells of bone marrow origin can be transfected, the Examiner has not pointed to any other features of the cells taught by Pullen et al. that are shared with the claimed cells. Pullen et al. never mentions transfected hematopoietic stem cells. On the contrary, Pullen et al. talks about macrophages. Pullen et al. suggests that the cells in their cultures are macrophages or committed macrophage progenitor cells, as their cultures produce bone marrow derived macrophages. These cell types are distinct from the cells encompassed by the pending claims.

The Examiner's argument rests on two references, neither of which disclose a transfected hematopoietic stem cell. As discussed above, one reference, Madsen et al., relates to L cells, which are fibroblasts. The other reference, Pullen et al., is concerned with macrophages. There is no motivation to combine the references. Even if one was to combine the references, and there is no motivation to do so, the combination would give a transfected L cell or a transfected macrophage, and not the cells of the invention. Furthermore, there is no suggestion to focus on MHC class I genes.

Claims 24-27 and 29-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen et al. in view of Pullen et al. as applied in the rejection discussed above, and in further view of Bernstein et al. The Examiner states that Bernstein et al.

> "supplements Madsen et al. and Pullen et al. by teaching that retroviral vectors, particularly Moloney-based retroviral vectors, can be used to introduce DNA into murine or human hematopoietic stem cells in culture...Bernstein et al. provides motivation for using retroviral vectors rather than other vectors known at the time of filing by teaching that the low frequency of stem cells in the hematopoietic system necessitates the use of highly efficient gene transfer techniques."

Applicant respectfully traverses this rejection. As discussed above, the primary references fail to suggest suggest the claimed hematopoeitic stem cells engineered to express a class I gene. The secondary reference, Bernstein et al., fails to add anything which would complete the combination. The Examiner has not pointed to motivation in Madsen et al. and Pullen et al. for choosing hematopoietic stem cells. Thus, one of skill in the art would not know to supplement these references with the teachings of Bernstein et al. Furthermore, Bernstein et al. fails to suggest transfection with MHC class I molecules.

In view of the discussion above, reconsideration and withdrawal of the rejection of the pending claims under 35 U.S.C. § 103(a) is respectfully requested.